ACUTE RENAL FAILURE

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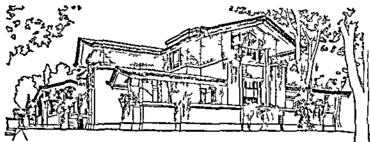
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ACUTE RENAL FAILURE

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Dedicated
to the memory of my father
Simon Grollman
1870 – 1952

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PREFACE

THE ONSET OF ACUTE RENAL FAILURE WAS LONG CONSIDERED a dire event and rightfully so since the majority of patients afflicted with the condition succumbed to its effects Inasmuch as the appearance of the kidney at autopsy in many of the patients revealed marked degenerative changes death was considered to have been inevitable and any treatment futile It is now realized however that the destruction of the tubules observed in patients dying in anuria is often reversible and if the patient survives the acute episode complete restoration of normal renal structure and function may occur

As a result of the wide interest in the pathogenesis and treatment of acute renal failure an extensive literature has accumulated which the author has attempted to correlate and interpret Special emphasis has been placed on the pathogenesis of the disorder and its treatment By anticipating its appearance the condition may often be averted when it appears proper management is essential for ensuring recovery from what may otherwise prove a fatal complication of a variety of disorders

Dallas Texas ARTHUR GROLLMAN

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ACUTE RENAL FAILURE

ONE

INTRODUCTION

THE KIDNEY PLAYS A VITAL ROLE IN MAINTAINING A CONSTANT internal environment of the organism not merely by its capacity to eliminate the waste products of metabolism but also in virtue of its regulatory processes whereby the volume composition and acid base equilibrium of the body fluids are maintained remarkably constant despite the perpetual impact of distorting factors [69, 86] In addition the kidney is concerned in the maintenance of the normotensive state and perhaps in certain metabolic functions When these varied activities are performed improperly the result is an **impaired renal function.** When there is a sudden and more or less complete cessation of this function the condition is designated as **acute renal failure,** which may be manifested as 1) a transient reversible impairment of short duration 2) a more prolonged failure accompanied by tubular necrosis and 3) the terminal stage of intrinsic renal disease

Acute renal failure may occur in the absence of intrinsic renal damage for example in circulatory failure in dehydration or in salt depletion—disorders which usually impair the circulation generally and the renal circulation in particular Extrarenal or **prerenal azotemia,** as this con

dition is designated is reversible and is remedied usually when the underlying condition responsible for the impaired circulatory state is corrected Under a variety of circum stances however either because of a delay in treatment or because of the severity of the impact on the kidney the con dition is not promptly reversed and a series of degenerative changes in the renal tubules follow which result in a failure of kidney function which may persist for several weeks A similar disintegration of the renal tubules may be induced by certain toxic agents It is this type of acute renal failure with which we are primarily concerned here

In addition to the two types of acute renal failure already described one encounters this condition also in association with **intrinsic renal disease** Thus in such chronic renal dis orders as chronic glomerulonephritis pyelonephritis or congenital malformations in which there is a progressive destruction of renal parenchyma the sudden superimposi tion of pathological processes elsewhere in the body with impairment of the renal circulation may also result in acute renal failure Other disorders in which there are alterations in the renal circulation such as eclampsia cortical necrosis necrotizing renal papillitis malignant hypertension and periarteritis are also characterized often by an abrupt sup pression of renal function

✓Acute renal failure may be defined accordingly as a disturbance in which as a result of toxic circulatory or other factors there is a sudden profound impairment or cessation of renal function Although originating as a result of the most diverse causes—trauma transfusion reactions poison ing crushing injuries hemorrhage postoperative shock hemolysis etc —the condition presents a distinct clinical syndrome with a definite pathologic pattern follows a well defined course and is amenable to certain specific forms of therapy There is however no sharp dividing line between

the serious sometimes irreversible forms of acute renal failure and the more benign and reversible transient renal failure observed in the so called extrarenal or prerenal azotemia The latter is remedied when the underlying condition responsible for the impaired renal circulation is overcome The intensity and duration of this circulatory failure determines whether there is simply an interruption in normal renal function that continues only so long as the factors tending to produce vascular collapse prevail or whether actual destruction of the tubular epithelium will result in renal failure that continues even after normal circulatory conditions are restored

Many terms have been used in the past to designate the syndrome under discussion These were based on assumptions which further experience has shown to be unfounded Thus the condition when observed following intravascular hemolysis was designated as **"hemoglobinuric nephrosis"**,[5] when it followed crush injuries it was designated as the **crush syndrome** [11] [5] Those instances of acute renal failure in which there is marked tubular degeneration are generally referred to as '**lower nephron nephrosis**, [40] a term which is inappropriate since in only some cases is the lesion confined predominantly to the distal portion of the nephron Since marked impairment of urine flow is a characteristic of the condition it is often designated as '**acute anuria**" [5] [87] However complete anuria is only rarely observed oliguria would be a more appropriate term but even with a normal urine flow renal function may still be markedly impaired The term acute renal failure describes the condition most appropriately

The course of acute renal failure may be divided into four stages 1) an initial episode in which the condition responsible for the development of the syndrome predominates 2) a period of anuria or oliguria 3) a period of

diuresis which initiates the first stage of recovery and 4) the final period of convalescence during which complete recovery takes place

TWO

ETIOLOGY

THE SPECIFIC CAUSES OF ACUTE RENAL FAILURE ARE legion In general however they may be classified into two main groups 1) conditions resulting in direct damage to the tubular epithelium as a consequence of poisoning by nephrotoxic agents and 2) those resulting in circulatory failure which gives rise to renal anoxia This circulatory failure may involve the general circulation which results secondarily in insufficiency of the circulation through the kidney[47] or it may represent a discrete interference with the renal circulation only

Nephrotoxic agents may cause acute renal failure through two mechanisms as described in the next chapter They not only may injure the renal tissue directly thereby impairing its function but may also exert their deleterious effects on the kidney through their action on the circulation The vomiting and diarrhea which is such a constant feature of metallic and other poisonings will if persistent result in circulatory insufficiency due to diminution of the extracellular and blood volumes It is this secondary effect of intoxications as well as the direct destructive action of the poison on the kidney which is often responsible for the observed renal failure in cases of poisoning

NEPHROTOXINS

The nephrotoxic agents which have been reported to induce acute renal failure are listed in Table I They are protoplasmic **poisons** *which are excreted through the kidney* where they exert their toxic action which results in renal failure In addition these agents often cause circulatory collapse as a result of the vomiting diarrhea and diuresis which they induce or as a consequence of the pooling of fluid outside vascular channels by their damaging effects on capillaries The damage exerted by these agents on other organs (heart liver brain etc) and tissues generally also serves as a subsidiary cause of shock which may contribute to renal failure

Sulfonamide intoxication (listed in Table I) differs from the other agents listed in that most cases of intoxication by this drug are a result of sensitization rather than of direct destructive action on the renal tissue In this respect acute renal failure secondary to sulfonamide intoxication bears a closer relationship to that seen in acute glomerular nephritis eclampsia and periarteritis rather than of the type due to other nephrotoxins The nephrotoxic action of **carbon tetrachloride** and of certain other organic toxins *differs also from that due to metallic poisons The latter* exert their action directly on the tubular epithelium the former induce severe interstitial edema and swelling This results in an interruption of the blood flow through the kidney which is responsible for the tubular damage which these agents induce

TABLE I

NEPHROTOXIC AGENTS CAUSING ACUTE RENAL FAILURE

I Metallic Poisons
Arsenic bismuth cadmium chromium gold lead mercury* uranium and salts of other heavy metals

II Organic Synthetic Compounds
Carbon tetrachloride[12] [13] diethylene glycol[14] sulfonamides[15] etc
III Inorganic Non Metallic Agents
Potassium chlorate bromates etc
IV Naturally Occurring Drugs and Organic Poisons
Mushroom poisoning pesticides etc

CIRCULATORY FAILURE

In addition to nephrotoxic agents acute renal failure may follow a great variety of apparently heterogeneous disorders These however have one common quality namely their tendency to cause vascular collapse and may be grouped accordingly on the basis of the recognized causes of circulatory failure *Such a classification is shown in Table* II Any condition conducive to severe and prolonged circulatory insufficiency will result in renal ischemia which in turn may induce renal failure of the type under consideration

Incompatible blood transfusions have been a frequent cause of acute renal failure Here renal ischemia may be attributed to the loss of oxygen carrying capacity of the blood as a result of hemolysis in the face of an already present anemia upon which is superimposed the shock attendant on the reaction Anoxia due to other causes (e g carbon monoxide poisoning pernicious anemia etc) may likewise act as etiologic agents

TABLE II

CIRCULATORY DISTURBANCES RESULTING IN ACUTE RENAL FAILURE

I Blood Loss[16]
1 Hemorrhage[16] [17]
a Trauma[18]
b Surgical procedures[19]
c Obstetric complications (utero placental separation postpartum hemorrhage)[20]

   2 Hemolysis[12]
      a Incompatible blood transfusions
      b Absorption of hypotonic fluids
      c Cold hemoglobinuria[60]

II Plasma Volume Loss
   1 Burns[33]
   2 Trauma (crush syndrome)[1, 21, 35]

III Extracellular Volume Deficits Due to Electrolyte Loss
   1 From gastrointestinal tract[38]
      a Persistent vomiting[43]
      b Diarrhea
   2 Segregated fluid accumulations
   3 Urinary losses[32]

IV Vascular Injury
   1 Infections[36]
   2 Acute nephritis
   3 Malignant hypertension[37]
   4 Toxemia of pregnancy[18]
   5 Eclampsia[19]

V Anoxia
   1 Carbon monoxide poisoning
   2 Anemia
   3 Cardiac failure
   4 Heat stroke
   5 Electroshock[29]

Circulatory insufficiency with resultant **renal ischemia** is often induced by loss of electrolyte and water such as is seen in persistent vomiting diarrhea or other causes of a deficient extracellular fluid volume This may be encountered as already mentioned in poisoning in acidosis alkalosis cholera diabetic coma Addison s disease gastro intestinal disturbances salt losing nephritis and other conditions tending to salt deficiency In most cases the renal failure so induced is immediately remedied when the deficit in extracellular fluid volume is corrected Only when extreme or prolonged does renal failure with persistent anuria persist even after the correction of the primary disturbance

Acute renal failure accompanies a group of conditions in which there is a release of massive amounts of pigment

into the circulation for example in incompatible blood transfusion blackwater fever (malaria) paroxysmal hemoglobinuria icterus (as in Weil s disease icterus neonatorum yellow fever hepatic necrosis etc) after massive burns and following the absorption of water when the latter has been used to irrigate the operative bed following prostatectomy The occurrence of acute renal failure under these conditions has been attributed to the presence of blood or muscle pigments in the tubules with the formation of casts which interfere with the flow of fluid through the tubular lumina to the action of hypothetical toxins originating in crushed tissues or to reflex circulatory disturbances interfering with filtration through the glomeruli However such factors have been discredited as causative agents of the observed renal failure The release of pigment per se is not of etiological importance in causing the renal failure in these cases although it may contribute to intensifying a condition primarily due to circulatory shock [7, 83]

Among the conditions in which acute renal failure is rarely observed are severe infections due to meningococcemia septic abortion typhus pneumonia etc and acute allergic states as in serum sickness sensitivity reactions to sulfonamides iodides bacterial toxins favism etc In these conditions the acute renal failure is partly attributable to circulatory shock and in part to vascular injury as discussed next

VASCULAR LESIONS

In addition to the acute renal failure which follows direct destruction of the kidney tissue by nephrotoxins and that which follows indirectly from circulatory failure one encounters this condition in cases where the primary injury is vascular affecting the blood vessels of the kidney particularly the glomerular tuft as in acute glomerular

nephritis or eclampsia the arterioles generally, as in periarteritis nodosa or interfering with the blood supply to the kidney as a result of interstitial swelling, as in necrotizing renal papillitis Some of the conditions already mentioned e g sulfonamide intoxication sensitivity reactions iodism infections etc also induce acute renal failure primarily by such effects on the renal vessels

Fundamentally regardless of whether the etiologic agent involves a general circulatory failure or specifically affects the renal vessels the same general result ensues viz anoxia of the kidney The last named as we shall see in the next chapter results in structural damage to the kidney comparable to that induced by the nephrotoxins It is not surprising therefore that such diverse agencies should all result in a syndrome conforming to a relatively unique clinical pattern

It is evident from the foregoing that acute renal failure may complicate almost any serious ailment The conditions mentioned either cause destruction of renal tissue directly or interfere with the renal circulation The manner in which this is brought about may differ but the end result in all cases is the same—viz an interference with renal function Despite its diverse origin from intoxications infections hemolysis surgical trauma etc acute renal failure follows the same clinical course with a period of oliguria or anuria following the precipitating episode and a period of gradual recovery of renal function in patients who recover

THREE

PATHOLOGY

PATHOLOGISTS FOR MANY YEARS HAVE OBSERVED THE widespread lesions encountered in the kidneys of patients dying in acute renal failure However they failed to recog nize the existence of any common underlying basis for the disorder and considered their findings in individual cases to be related to some specific pathologic pattern Thus the observation of pigment casts in cases of hemolytic reactions gave rise to the description of hemoglobinuric nephrosis as a pathologic entity the lesions induced by sulfonamide intoxication as the sulfonamide kidney that seen in trau matic injury as the kidney of the crush syndrome [18] The lesions induced in the kidney by nephrotoxic agents were regarded in turn as separate entities The relation of the observed pathological lesions to the functional disturbances which they induced was not appreciated nor was the course of acute renal failure resulting from such diverse causes recognized as following a definite pattern

Among the noteworthy earlier studies of the pathologic appearance of the kidney in acute renal failure was the monograph of Suzuki [90] which appeared in 1912 This described in detail the localization of the tubular lesions associated with a number of nephrotoxic agents but his

claims regarding the specific localization of these lesions in the proximal tubule were denied by subsequent workers Interest in the pathogenesis of the anuria associated with the crush syndrome observed in victims of bombing during World War II led to the description by Dunn and his collaborators[25] of the severe lesions in the distal tubule observed in patients dying of renal failure following a crushing injury A more extensive study was reported by Lucke[49] in 1946 which aroused widespread interest and inaugurated the studies which have led to our present day concepts in this field

Lucke s unique contribution consisted in his emphasis on the common features of a variety of different disorders all of which terminated in acute renal failure He demonstrated that many conditions—shock trauma, burns intoxications transfusion reactions, etc —resulted in an identical pathologic pattern rather than in separate entities as previously believed Lucke also demonstrated that the renal lesion although devastating during the early stages of anuria was reversible and that if the patient survived for a time complete regeneration of the kidney was possible This observation stimulated interest in the therapeutic management of a disorder considered previously as invariably fatal Lucke described the lesion as involving predominantly the distal portion of the nephron which led him to designate it by the alliterative term **"lower nephron nephrosis"** which immediately received wide acceptance However as already indicated this term is inappropriate since the lesion is not always limited to the lower nephron nor is it a ' nephrosis in the sense that this term is used clinically Despite the criticisms leveled at the term lower nephron nephrosis " the significance of Lucke s fundamental contributions cannot be overemphasized

The recent studies of Oliver McDowell and Tracy[57] have

clarified the problem of the pathologic lesions occurring in acute anuria and harmonized the discordant work of previous workers These authors by utilizing the technique of dissecting and examining whole nephrons avoided the uncertainties involved in localizing the lesions by conventional cross sections of the kidney Moreover by a careful analysis of the lesions induced by nephrotoxic agents and those observed following circulatory disturbances Oliver and his associates demonstrated that these two types of conditions induce fundamentally different morphologic disturbances However because of the concomitant occurrence of circulatory disturbances in many cases of poisoning the two types of lesions are often associated The following description summarizes the findings and conclusions of Oliver and his associates

EFFECT OF NEPHROTOXINS

The lesions induced by nephrotoxic agents are limited usually to the proximal convolution and are evenly distributed throughout all the nephrons Poisons having gained access to the circulation evidently reach all the nephrons simultaneously and damage the first portion of these with which they come in contact viz the **proximal convolution** either by absorption from the blood or from the glomerular filtrate As a result of their destructive action the nephrotoxins induce a degeneration of the tubular epithelium which ultimately sloughs off from its basement membrane which usually remains intact[47]

In addition to the characteristic lesion induced by nephrotoxins one may observe also in some cases of poisoning the lesion characteristic of renal ischemia (described next) since poisoning is accompanied often by circulatory shock The lesion limited to the proximal tubule is observed chiefly in poisoning by metallic salts and other chemicals which

are excreted in the urine and thus gain access to the tubular epithelium In poisoning by many organic compounds on *the other hand the lesion is identical with that resulting* from ischemia or from processes involving primarily the blood vessels of the kidney In carbon tetrachloride poisoning[83, 85] for example the lesion involves primarily the lower nephron and resembles that resulting from renal ischemia as described in the next section This poison causes severe interstitial edema and inflammatory swelling of the kidneys which apparently reduce the blood flow through the kidney by compression of the renal vessels and thus induces renal anoxia comparable to that observed in circulatory failure Persistent vomiting also frequently follows carbon tetrachloride and other organic poisonings which contributes further to the renal anoxia

It is not surprising therefore that the renal lesions following intoxication with these nephrotoxins resembles that of circulatory shock rather than of the metallic and other specific renal toxins That this shock rather than any specific *nephrotoxic action is the cause of the observed renal* damage was shown for example by Berg Levinson and Wang[6] in *Clostridium perfringens* poisoning in dogs By applying a plaster cast following the injection of this toxin into dogs circulatory failure was prevented and the urinary output maintained

LESIONS RESULTING FROM ISCHEMIA

The lesions characteristic of circulatory failure (termed **"tubulorhexis"** by Oliver) differ in their distribution among nephrons and within a single nephron from the nephrotoxic lesions In contrast to the latter the tubulorhexic lesions are distributed at random from the proximal convolution adjacent to the glomerulus to the collecting tubule Moreover entire nephrons *even in markedly damaged kidneys*

may remain unaffected and maintain their integrity as do also the undamaged portions of involved nephrons The lesion as in the case of nephrotoxins consists of degeneration and desquamation of the epithelial lining of the involved portions of the tubules of the affected nephrons In case of profound damage disruption of the basement membrane may ensue as a result of which the lumen of the tubule becomes continuous with the interstitial tissue This results in a tubulo venous anastomosis which permits passage of the glomerular filtrate from the lumen of the tubule back into the blood stream In the unaffected nephrons even the mitochondrial elements which are delicate indicators of cellular integrity appear normal

The glomeruli appear structurally to be intact However they perhaps do not retain their normal degree of impermeability since they permit the passage of large amounts of protein which appears as casts in the tubules The collecting tubules also escape damage except for occasional areas of desquamation but often are filled with casts and debris originating in the more proximal portions of the nephron These casts and accumulations of heme pigment have attracted considerable attention because of their prominence in sections of the kidney (cf Figure 1) and have even been considered responsible for the observed anuria However as shown by Oliver [67] these casts do not appear to exert any noteworthy blocking action since portions of the tubules proximal to the casts are not usually dilated Moreover since many nephrons contain no casts it is difficult to ascribe much significance to their presence

The interstitial tissue surrounding the ruptured tubules is often edematous and may be infiltrated by monocytes and polymorphonuclear cells At a later stage there is a proliferation of capillaries with the formation of granulation tissue in the affected areas

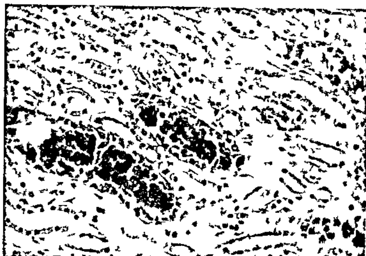


Figure 1 Microphotograph of a section of the kidney from a patient dying in acute renal failure following an incompatible blood transfusion Note the collections of heme casts in the lumina of the tubules and the degenerative changes of the epithelial cells lining the distal tubules

The random distribution of the tubular lesions observed in circulatory shock as opposed to the universal but limited distribution of the lesions in cases of nephrotoxins is to be anticipated from their vascular origin The nature of the intertubular circulation is such that an interference with the blood supply to the kidney must of necessity affect all parts of the nephron and therefore eventuate in a haphazard distribution of the lesions within any given nephron Any part of the nephron may accordingly be affected in circulatory shock while certain entire nephrons and portions of damaged nephrons may remain intact [24, 79]

REGENERATION OF DAMAGED NEPHRONS

Much emphasis has been placed on the capacity for regeneration of the nephron in cases of acute renal failure Even

in fatal cases this regeneration is apparent in sections of the kidney (cf Figure 2) However as shown by Oliver et al [61] this regeneration is not always complete throughout the length of the nephron Irreparable injury may persist which prevents the nephron from resuming its normal function In the case of nephrotoxic damage in which the epithelial cells only are desquamated complete regeneration is possible but when as in the case of the ischemic lesion the basement membrane is also disrupted no directing surface remains on which regenerating epithelial cells may reform the tubule The breach in the tubular wall in such cases is invaded by interstitial granulation tissue which fills the lumen of the tubule Despite active regeneration of the tubular epithelium restitution of the integrity and normal functional capacity of the nephron may accordingly not be possible Lacking the support and guidance of a basement membrane the regeneration of epithelium is often disordered and functionally useless The haphazard growth of epithelium may actually occlude the tubular lumina Only in less severely damaged nephrons can restitution of normal function occur This is of fundamental importance from the standpoint of prognosis for it has been claimed by many that no patient suffering from acute renal failure need die of renal insufficiency if he be tided over the period necessary for regeneration of the tubules Apparently in cases of severe damage restoration of normal function may be impossible

It is also to be emphasized that in the case of regenerated tubules the presence of even a small area of discontinuity will interfere with the normal function of the involved nephron The existence of such scattered nephrons may account for the prolonged appearance of albuminuria and other evidence of impaired renal function in patients who have recovered from acute renal failure [45] [83] The ultimate

disappearance of these abnormal findings may result from the obliteration of such damaged nephrons and their replacement by scar tissue

Regeneration of the tubular epithelium is evident in patients dying within a few days of the onset of acute renal failure In those who survive a week the repair is fairly complete which is in accord with the observed diuresis which takes place at about this same time

Figure 2 illustrates the characteristic features of the tubular degenerative and regenerative changes occurring in acute renal failure It shows the appearance of the kidney



Figure 2 The appearance of the kidney in acute renal failure Section of the kidney from a patient dying in acute renal failure 16 days after a gun shot wound through the aorta Note that the lesion is limited to the distal tubule and represents accordingly an instance of lower nephron nephrosis Areas of regenerated tubules are present as well as those in which the epithelium has desquamated The glomeruli are intact ×190

of a patient who died 16 days following a gunshot wound through the abdominal aorta The patient suffered a pro longed period of hypotension before the lesion in the aorta could be repaired and his blood volume replenished The section shows areas of denudation of the epithelium involv ing primarily the distal tubules as well as regeneration of the affected nephrons

EXPERIMENTAL STUDIES

The widespread structural lesions observed in the kidney in patients dying of acute renal failure have been reproduced experimentally by clamping the renal artery of dogs[7] and rabbits[5] and by traumatic injury resulting in renal ische mia[73] The lesions induced by these methods were found by Oliver and his colleagues[67] to show the same irregularity of distribution of the tubular damage as is observed in the human in the so-called crush (Bywaters) syndrome Even in cases of minimal interference with renal function the actual damage to the affected nephrons was profound The severity of the process as judged from renal function studies is determined apparently by the number of nephrons affected rather than by the severity of the damage if this is limited to a few nephrons In the case of nephrotoxic tubu lar damage where all nephrons are affected equally it is the degree of damage to each nephron that determines the extent of the interference with renal function

VASCULAR LESIONS

Acute renal failure as indicated in the previous chapter is also observed in conditions in which there is a discrete obliteration of segments of the renal circulation For ex ample in sulfonamide sensitization acute glomerulone phritis eclampsia periarteritis and malignant hyperten sion the lesions in the kidney are primarily vascular in

origin involving the smaller blood vessels or the glomerular tufts To what extent these lesions are responsible for the observed renal failure and the role played by other factors present in these disorders in inducing the observed failure has not been established However although desquamation of the tubular epithelium, such as is noted following nephro toxins or circulatory failure may not be apparent degen erative changes in the tubules are commonly noted Like wise in acute necrotizing papillitis[83] and in cortical necrosis of the kidney[82] degenerative changes in the tubules are demonstrable These changes as well as the interference with the blood supply to the tubules interfere with tubular function as shown in the next chapter and result in the same clinical pattern as that seen in the classical lower nephron nephrosis

FOUR

PHYSIOLOGY

THE WIDESPREAD STRUCTURAL DAMAGE TO THE NEPHRON described in the preceding chapter results in profound functional disturbances The formation of urine by the kidney consists essentially in 1) glomerular filtration 2) tubular secretion and 3) active and passive tubular re absorption Normally approximately 190 liters of ultra filtrate per day (glomerular filtration rate in the adult male as measured by the clearance of inulin) are formed in the glomeruli Of this large volume of fluid about 85 per cent is reabsorbed in the proximal tubule with the production of an iso-osmotic solution which is subjected to further al teration as it passes through the remainder of the tubule It is apparent therefore that any widespread injury to the renal tubules will impair profoundly their capacity to elabo rate urine Alterations in the glomerular filtration rate will be less critical and indeed unless markedly decreased may not seriously interfere with renal function On the other hand reduction in the blood flow through the kidney will exert a fundamental influence since this will affect not only the filtration process through the glomeruli but also the blood supply to the tubules which is so essential for their normal function [86]

RENAL PLASMA FLOW

The normal rate of *blood flow through the kidney is* approximately a liter per minute Conditions causing circulatory insufficiency result in a marked diminution in the rate of this flow a decreased rate of glomerular filtration and renal ischemia If the latter is profound or prolonged the tubular disruption described in the preceding chapter will ensue This reduction in the renal plasma flow is not limited merely to the period of circulatory shock which precipitates the onset of acute renal failure but tends to persist for some time after the circulatory insufficiency is corrected [1 40 81 96]

The decrease in renal plasma flow accompanying acute renal failure has been demonstrated experimentally as well as in the human patient Thus Phillips Van Slyke et al [71] observed that hypotension and shock induced in dogs by hemorrhage was accompanied by a decrease in the rate of the renal blood flow which ceased completely when the hemorrhage was massive In uranium poisoning in dogs the *renal plasma flow (as measured by diodrast clearance) is* also reduced [8] Apparently in circulatory failure the blood normally flowing through the kidney is diverted to more vital organs [80 88] This reduction in renal blood flow occurs even in cases where the trauma is of a degree insufficient to induce structural damage to the renal tubules [40 72]

Results comparable to those observed in the experimental *animal have been noted also in the human subject Thus in* thirty five patients suffering from skeletal trauma hemorrhage peritonitis burns and head injuries studied by Lauson Bradley and Cournand[47] the renal blood flow and filtration rate were found to be decreased in proportion to the degree of shock The renal function in patients not in shock remained normal as did also the filtration fraction Except in cases of head injury there was a *shunting of*

blood from the kidneys with a good correlation between the renal blood flow and the blood pressure and cardiac output Following transfusion the filtration rate increased *concomitantly with the rise in arterial blood pressure* but the renal blood flow tended to remain low or fell after a temporary rise The renal vasoconstriction thus appears to *persist in shock even after restoration of the blood pressure* to normal However in none of the patients of this series was there persistent oliguria or anuria since the circulatory shock *was promptly corrected* The ischemia of the kidney interfered temporarily with renal function but was too transient to induce structural damage to the nephron

Results similar to those just described were also obtained by Burnett and his colleagues [12] Following severe trauma these observers noted a reduction in the filtration rate (mannitol clearance) and renal plasma flow (para amino hippurate clearance) but no interference with maximum tubular capacity to excrete para aminohippurate Apparently during the early stages of trauma there is only a reduction of glomerular activity secondary to decreased renal blood flow *Others have noted similar effects following* sulfathiazole and carbon tetrachloride intoxication embolism peritonitis and the removal of occlusive cuffs to the extremities [43, 45, 81, 7, 86]

The consequence of the reduction of renal plasma flow as just described is twofold it leads 1) to a reduction in the glomerular filtration rate and 2) to renal ischemia which interferes with tubular function and permits back diffusion of the glomerular filtrate Circulatory shock by causing a diversion of blood from the kidney leads to ischemia of this organ this is responsible for the oliguria and other defects in renal function observed during the period of shock If this ischemia is corrected promptly the interference with renal function is temporary if the ischemia

persists necrosis of the tubular epithelium results and a protracted period of oliguria ensues

CONSEQUENCES OF TUBULAR DEGENERATION

The tubular degeneration occurring as a result of nephrotoxins or prolonged circulatory failure leads to a complete abeyance of renal function The glomerular filtrate no longer comes in contact with actively functioning tubular tissue Instead it passes along the basement membranes (which in certain areas may also be interrupted) of denuded tubules and passively diffuses back into the blood stream Only in the few remaining intact nephrons will the formation of urine continue which accounts for the fact that oliguria rather than complete anuria is usually observed

As a result of the cessation of the formation of urine the normal **composition** of the blood and other body fluids is disordered due to the accumulation of metabolic products which can no longer be excreted Urea uric acid creatinine and other non protein nitrogenous constituents of the blood accumulate and their concentration in the blood rises progressively However there is no good evidence to indicate that these catabolites in the concentrations ordinarily encountered in acute renal failure exert any obvious deleterious effects although their presence may accentuate the degree of anemia or vascular injury seen after extended periods of renal failure [59, 60]

Cellular breakdown is also responsible for the progressive accumulation of sulfate inorganic phosphate and other fixed acids which displace bicarbonate and give rise to a progressively increasing acidosis and a lowered bicarbonate concentration of the blood This is of little consequence unless sufficiently marked to give rise to respiratory difficulty

Insofar as the composition of the blood is concerned the most critical change of practical significance is the alteration

in the concentration of potassium [26] With normal renal function the serum concentration of this ion is maintained between 3 7 and 5 3 milliequivalents per liter but in acute failure abnormally low as well as toxic high levels are encountered Several factors tend to increase the potassium content of the blood The breakdown of protein results in the liberation of potassium in a fixed ratio to nitrogen This breakdown is accentuated by injury and by starvation factors which complicate patients in acute renal failure Moreover hypertonicity of the cellular contents which as shown below may occur in renal failure also tends to cause a shift in potassium from the intracellular to the extracellular compartment [23 27 28]

Counteracting the above-described tendencies towards hyperpotassemia are several factors which cause a shift of potassium from the extracellular to the intracellular compartment The utilization of carbohydrate anabolic processes expansion of the extracellular fluid by the injection of potassium free fluids and losses of potassium from the gastrointestinal tract all tend to reduce the potassium concentration of the blood which may eventuate in hypopotassemia The ultimate potassium concentration of the blood may thus be abnormally low or high depending on the relative preponderance of the various factors just considered and the amount of potassium which is ingested If the serum potassium concentration deviates appreciably from normal the signs and symptoms of hyper or hypo potassemia described in the next chapter will ensue

In addition to the abeyance of the excretory function of the kidney acute renal failure is accompanied by a cessation of the other regulatory functions of this organ This may result in deviations of the normal volume and tonicity of the body fluids if the intake and loss of salt and water are not balanced In the absence of normal renal function such dis

tortion induced for example by vomiting diarrhea or the injudicious administration of salt or water cannot be corrected as they are in the normal As a consequence dehydration overhydration salt depletion or edema will appear depending on whether there is a deficit or excess of water or salt or of both of these constituents

In addition to the above mentioned consequences of acute renal failure the normal action of the kidney on the cardiovascular system will be in abeyance as a result of which the blood pressure will tend to rise and ultimately necrosis of the blood vessels smooth muscle generally and of the myocardium ensue The role of the kidney in the pathogenesis of these cardiovascular effects was noted first in the nephrectomized animal [35, 36, 61] However similar observations have been made in human patients dying in acute renal failure [59]

FUNCTIONAL DEFICIENCIES OF THE REGENERATED TUBULES

Even with complete regeneration of the tubular epithelium which begins soon after the onset of anuria recovery of renal function remains inadequate The newly regenerated tubules only gradually resume their normal capacity to form a concentrated urine [55, 74] Immediately following the period of anuria or oliguria there is a period of diuresis during which as much as ten or more liters of dilute urine are excreted daily (cf Figure 3) This abnormal rate of urine flow reflects the loss of concentrating power by the newly regenerated tubules [75] The kidney during this period is unable to conserve water for even if water be withheld from the patient the volume of the urine remains high and the loss of water continues with resulting dehydration That this loss of water is not due to a deficiency of the antidiuretic hormone is shown by the poor response to injected posterior

uitary liquid The tubules at this period are unable ap
rently to manifest their usual response to this hormone
Not only are the newly regenerated tubules unable to con
ve water but they are also incapable of conserving
lium and chloride As a consequence there is a loss of
t from the blood ("salt wasting syndrome") This may
ntinue for a period of a week to several months

Despite the large volumes of fluid excreted during this
riod of diuresis the non protein nitrogen urea and
eatinine concentration of the blood may decline only
wly over a period of days or weeks (cf Figure 3) This
lay as well as the tendency to lose salt and water indicates
at abnormal tubular back diffusion exists even when the
bules appear structurally to be intact That such back
fusion occurs has been demonstrated by several groups
investigators[8, 18, 42, 63, 78, 83]

During the final recovery stage of acute renal failure
ere is a gradual resumption of normal renal function
zotemia gradually disappears the blood pressure declines
its normal level acid base balance and the volume and
mposition of the cellular and extracellular compartments
e restored to normal The tubules have now recovered
eir normal functional capacity

OTHER FACTORS IMPLICATED IN ACUTE RENAL FAILURE

veral other explanations have been offered for the ob
rved failure of the kidney in circulatory shock In order
account for the observed oliguria Truetta and his col
agues[83] postulated a neurogenic mechanism whereby the
ood was shunted from the active filtering and secreting
rtex of the kidney to the poorly functioning outer medul
ry zone However the "Truetta phenomenon" which fol
ws *traumatic injury stimulation of the nervous system or*

the injection of epinephrine involves only the superficial vessels of the kidney There is no actual shunting of blood from the cortex to the intermedullary zone but merely a cessation of blood flow through the peripherally located terminal branches of the interlobular arteries with blanching of the surface of the kidney The existence of a true shunt as envisaged by Truetta in which the renal cortex is rendered ischemic before the deeper layers of the kidney are affected has not been substantiated [67, 86]

Collections of pigment are commonly seen in the lumen of the tubules in patients dying in acute renal failure (Figure 1) Their frequent occurrence has suggested that the anuria observed in such cases is attributable to obstruction by such pigment The presence of pigment casts in the distal tubule is particularly common in patients dying in acute renal failure following intravascular hemolysis (as in incompatible transfusion) in blackwater fever favism clostridia infection and other conditions where hemolysis occurs However the injection of purified cell free homologous pigments both in man and in the experimental animal and even the injection of the debris of laked cells in the latter induce no vasomotor reactions nor any interference with renal function [7, 10] Only where factors are present which impair circulatory efficiency such as dehydration salt depletion histamine shock or the like do hemolytic phenomena eventuate in acute renal failure [53] Injury of the proximal tubule may however occur as a result of athrocytosis[73] as is the case in animals injected with excessive amounts of hemoglobin [31] In the human however where pigment formation never reaches these amounts it is unlikely that the constantly observed pigment casts ever contribute to the renal failure

FIVE

CLINICAL COURSE

IN VIEW OF THE MULTIPLICITY OF THE FACTORS RESPONSI ble for the development of acute renal failure the course and management of the syndrome during its earliest phase will obviously vary During this period the usual features of shock are encountered with the signs and symptoms of circulatory collapse These are the same irrespective of their cause To these however are added certain specific features characteristic of the initiating cause of the collapse and renal injury The primary disorder may continue to act long after the onset of renal failure For example in case of carbon tetrachloride poisoning jaundice and other evidence of liver dysfunction may subsequently make their appear ance

EARLY SYMPTOMS

The clinical features of the early stages of acute renal failure are usually overshadowed by the primary condition respon sible for the disturbance in kidney function The onset of oliguria in fact may be overlooked in the face of the more alarming manifestations Abnormality in the appearance of the urine for example its discoloration by blood or other

pigments is more apt to attract attention than a marked reduction in urinary output

Nausea and vomiting are prominent early symptoms of acute anuria and may be encountered regardless of whether or not shock is present Weakness malaise pain in the abdomen or back are also frequently noted at the time oliguria or anuria is first noticed Insatiable thirst is often present when the blood volume is reduced or its tonicity raised acutely This is noted particularly in carbon tetra chloride poisoning severe burns and pre eclampsia ' Satis faction of this thirst frequently leads to vomiting with the further loss of salt With unlimited access to water hyponatremia results with ultimate development of water intoxi cation and edema which may be apparent when the patient is first seen

The symptoms manifested by patients during the early days of acute renal failure are determined primarily by the treatment to which they are subjected When properly controlled the patient presents a minimum of symptoms *after the primary condition responsible for the renal failure* has been corrected The blood pressure will have returned to its normal level and the patient may appear superficially to be in excellent condition except perhaps for weakness and anorexia

Should the patient be managed injudiciously during the early stages of oliguria by the administration for example of excessive amounts of saline or water or given access to foods rich in potassium or protein or should vomiting or diarrhea result in a loss of extracellular fluid the effects of these will of course predominate Massive injections of saline will lead to generalized edema Free access to water may result in hyponatremia and the development of a firm *generalized edema tearing salivation nausea apathy* and the other symptoms of water overload Vomiting and diar

thea may result in salt deficiency with hypotension and other symptoms of extracellular volume deficit The management of these complications is discussed in the next chapter

PERIOD OF OLIGURIA

The urinary suppression observed in acute renal failure begins with the onset of circulatory shock and varies from complete anuria in more severe cases to varying degrees of oliguria This is accompanied by a gradual rise in the serum concentrations of urea creatinine uric acid non protein nitrogen fixed acids (sulfate phosphate) phenol and other normally excreted catabolites The rate at which this rise occurs varies being dependent on the relative rates of endogenous protein anabolism and catabolism In patients with obstruction of the ureters due to invasive carcinoma for example the rise in serum urea nitrogen under optimal conditions may be slow (about 10 mgms per cent per day) On the other hand following trauma or other conditions characterized by massive tissue destruction this rise may be precipitous (100 to 200 mgms per cent per day) Subsequently as the stresses responsible for this rapid rate of cellular breakdown disappear the rate of rise in the non protein nitrogen concentration of the blood declines

The accumulation of non protein nitrogenous compounds and other products of cellular breakdown give rise to no remarkable symptoms during this period On the other hand the alterations in the serum potassium concentration as described in the preceding chapter may give rise to a train of signs and symptoms associated with potassium intoxication or deficiency depending on the serum concentration (not the cellular content) of this ion **Hypopotassemia** (at serum concentrations below 3 meq per

liter) is manifested by weakness of the skeletal muscles which when extreme gives rise to a flaccid paralysis There is decreased motility of the gut (adynamic ileus) with ab dominal distention nausea and vomiting Weakness of the respiratory muscles interferes with their normal activity and results in dyspnea with gasping respiration and cyanosis Impaired cardiac function is manifested in alterations of rhythm and the strength of myocardial contraction These give rise to cardiac dilatation the appearance of systolic murmurs tachycardia an elevated venous pressure and other signs of cardiac failure The **electrocardiogram** will show prolongation of the Q T interval depression of the S T segment and a decrease in amplitude and broadening of the T waves It should be emphasized however, that the electrocardiogram although suggestive is not a specific in dicator of the degree of hypopotassemia For its detection one must rely on chemical analysis of the serum

Hyperpotassemia (with serum potassium levels above 5 5 meq per liter) also causes symptoms referable to the neuro muscular system The condition causes paresthesias and flaccid or myasthenic paralysis of the skeletal muscles The patient becomes listless and mentally confused The blood pressure declines to hypotensive levels and there is evidence of peripheral vascular collapse The **electrocardio gram** reveals tall peaked T waves depression of the S T segment decrease in size with ultimate disappearance of P waves and lengthening of the QRS and PR intervals Auricular standstill is followed by heart block and total arrhythmia progressing to cardiac arrest The electrocardio gram is more pathognomonic of hyperpotassemia than of hypopotassemia

PERIOD OF DIURESIS AND RECOVERY

The period of anuria or oliguria usually lasts from three to 10 days but in exceptional instances has lasted as long as 25 days with ultimate recovery of the patient. A typical response is shown in Figure 3 in which anuria lasting eight

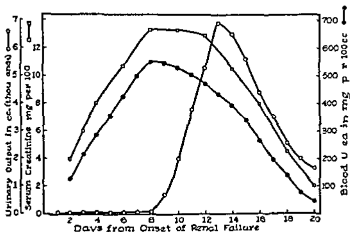


Figure 3. Curves showing the typical course of the urinary output and azotemia in a patient suffering from acute renal failure following carbon tetrachloride intoxication. Diuresis set in abruptly after nine days of oliguria but regression of the concentration of the urea and creatinine of the blood did not begin until the diuresis began to subside.

days followed carbon tetrachloride poisoning. At the conclusion of the period of oliguria or anuria, diuresis may set in abruptly, as shown in Figure 3, or gradually over a period of several days. During this period, clinical improvement may not be apparent and the patient's condition may actually worsen with the appearance of confusion, vomiting, abdominal cramping, areflexia and increasing azotemia

These adverse responses as shown in the preceding chapter are a consequence of depletion of the extracellular fluid as a result of the failure of the kidney at this time to conserve salt and water and form a concentrated urine

As renal function is restored the diuresis gradually recedes azotemia slowly declines and complete restoration of renal function again maintains homeostasis The time necessary for the non protein nitrogen concentration to return to normal following the onset of diuresis may vary from one to five weeks A sudden drop in the urinary output will occur if the intake of salt and water lags behind the output **Infection,** particularly of the kidney will also cause a cessation or diminution of the diuresis The patient must be carefully scrutinized for the appearance of these complications and the appropriate measures taken promptly to counteract them

CARDIOVASCULAR COMPLICATIONS

Throughout the oliguric as well as the diuretic and recovery phases of acute renal failure various cardiovascular complications may appear These are a consequence of 1) disturbances in the salt and water exchange 2) hyper or hypopotassemia and 3) the abeyance of the normal renal *regulatory action on the circulation* Disturbances in salt and water exchange result in distortion of the vascular and interstitial volume which in turn affect the circulatory dynamics The effects of alterations in serum potassium have already been discussed in the preceding section The **blood pressure** usually rises during the oliguric phase often to hypertensive levels and may not decline to normal for several weeks or months This rise represents probably true renal hypertension resulting from derangement of that function of the kidney which maintains the normotensive state [35] [36] In patients dying in acute renal failure vascular

lesions comparable to those observed in the nephrectomized dog may be noted [59]

The chief complication occurring during the anuric period is heart failure This complication is heralded by an acute rise in blood pressure the appearance of rales in the lungs a systolic murmur due to functional mitral insufficiency and gallop rhythm Patients in acute renal failure are also notoriously liable to acute pulmonary edema which may occur at any stage of the disorder and even under conditions in which overloading of the circulation has been carefully avoided The cause of this disturbance has been the subject of conjecture It is most probably due to myocardial damage induced by renal failure and comparable to that described in the dog following nephrectomy [56, 61, 6]

Anemia of moderate degree frequently develops during the course of acute renal failure This anemia is in part a result of suppression of hematopoiesis and in part due to an hemolytic process similar to that seen in chronic nephritis and observed experimentally following nephrectomy [60] Profound anemia in which the red blood count drops suddenly as a result of an acute hemolytic process may occur usually during the second or third week following the onset of anuria

SIX

TREATMENT

THE EARLIEST ATTEMPTS AT THE THERAPEUTIC MANAGEMENT of acute renal failure were in the light of our present knowledge misguided and resulted in harm rather than in an amelioration of the condition They consisted in the use of diuretics and the forcing of fluids in the hope of initiating diuresis Such procedures were obviously futile considering the underlying pathological condition since they depend *for their action on the presence of an intact functional* tubule They led only to expansion of the extracellular fluid volume and eventuated in edema or waterlogging and ultimately hastened death by inducing pulmonary edema

Decapsulation of the kidneys which aimed at relieving tension within the organ is also now recognized as an irrational and futile measure and potentially harmful adding as it does the shock of an operative procedure [97] **Sympathetic blockade,** induced by the administration of procaine or infiltration of the splanchnic nerves was advocated on the assumption that anuria was the result of vasoconstriction or the diversion of blood from the cortical glomeruli (Truetta phenomenon) The error of these assumptions is now recognized [45, 0, 86] Their use involves the potential danger of inducing hypotension thereby further reducing

the renal blood flow and increasing the degree of renal ischemia

The modern management of acute renal failure consists primarily of 1) prophylactic measures during the shock stage in order to prevent the onset or at least to mitigate the renal disturbance responsible for the syndrome 2) maintaining as normally as possible the volume and composition of the body fluids and restraining tissue breakdown to a minimum during the period of anuria and diuresis and 3) the use of artificial measures occasionally as temporary expedients to replace the defective renal excretory function

The management of the patient during the immediate period following any of the conditions which cause acute renal failure is of paramount importance for it is during this period that the degree and reversibility of the renal lesion is determined and extrarenal damage to the organism occurs During this period all available measures should be taken to prevent circulatory failure prolonged hypotension and anoxia which result in disruption of the tubules and the development of acute renal failure In fact with proper management acute renal failure may often be avoided if the conditions causative of this syndrome be kept in mind and promptly overcome Anuria having set in conservative management will usually suffice to tide the patient over until recovery of renal function ensues Only in a small percentage of patients and in those who have been mismanaged or in whom complications supervene is it necessary to resort to the use of the artificial measures to be described later

PROPHYLACTIC MEASURES

As has already been emphasized acute renal failure results from conditions which induce anoxia of the tubules which

in turn leads to the tubular dysfunction responsible for the observed anuria or oliguria Obviously measures which mitigate the effects of nephrotoxins and which counteract circulatory failure will prevent or at least reduce to a minimum the anoxia of the tubules which is responsible for the appearance of the syndrome The procedures now to be considered consist of certain specific measures which will vary depending on the nature of the primary disturbance and general measures to be applied irrespective of the causative agent

In cases of **poisoning,** measures should be directed towards 1) the removal of the toxin from the body if possible 2) the administration of specific antidotes when *available and 3) the use of measures to overcome circulatory* shock and to replace the loss of body fluids The induction of emesis gastric lavage and in some instances *peritoneal lavage* may remove some of the poisonous agent and prevent a lethal outcome Of the **specific antidotes,** mention may be made of dimercaprol (Bal) in mercury and arsenic poisoning methylene blue in methemoglobinemia nitrites and thiosulfate in cyanide poisoning central nervous stimulants in barbiturate poisoning depressants in strychnine poisoning and allyl nor morphine in opiate poisoning These measures having been taken attention should be directed towards the general measures now to be described

Because of the emphasis which has been placed in recent years on the danger of overloading the circulation by the injudicious use of saline infusions there has been a tendency to follow the opposite, equally undesirable and harmful procedure viz to permit depletion of the extracellular fluid and thereby perpetuate circulatory failure and renal anoxia This is particularly true in conditions such as poisoning in which there is a marked loss of salt through

vomiting diuresis diarrhea and the segregation of fluid in areas of capillary damage Prompt administration of parenteral fluids to compensate for these effects is desirable The beneficent effect of fluid therapy in mercury poisoning was noted indeed many years ago before the pathogenesis of the underlying process had been clarified [4]

Since hemorrhage is a common cause of circulatory failure the liberal use of transfusions to compensate for blood loss is indicated However blood transfusions not only serve to combat the onset of acute renal failure but are also a frequent cause of this syndrome due to incompatibility or the presence of isoaglutinins Under such conditions there is often a psychological barrier to the further use of transfusions This must be overcome and carefully matched blood used to remedy the shock induced by the reaction and to correct for the anemia for which the original transfusion was given Where plasma is not needed and there is danger of overloading the vascular system packed red cells should be used if the hemoglobin content of the blood is adequate plasma should be administered

Having replenished the vascular system with blood and plasma attention should be directed to the need for salt and water The form in which these are to be administered must be evaluated judiciously in terms of the tonicity volume and composition of the extracellular fluid This correction of the abnormal volume and composition of the body fluids must be made precisely since in the abeyance of renal activity the automatic adjustment of these variables by the kidney is impossible Unfortunately no simple practical measure is available for the rapid determination of the extracellular fluid volume One must rely accordingly on the history clinical signs and symptoms for its evaluation A history of vomiting or diarrhea for example will suggest deficit of extracellular salt and water the existence of pit

ting edema an expansion of the extracellular space dehydration a salt and water deficit

The serum concentration of chloride bicarbonate sodium and potassium may be rapidly measured by modern methods Such data are essential for the accurate determination of the salt requirements of the patient In diseased conditions such as acute renal failure the sodium cannot be estimated accurately from the chloride concentration nor from the sum of chloride plus bicarbonate as is the case in normal subjects [69] It must be remembered also that a large deficiency of sodium in the body causes only a relatively small deficit in the concentration of this ion in the serum Moreover the volume of the extracellular fluid as well as the concentration of sodium must be taken into account in determining the content of this ion in the extracellular fluid If the volume of the extracellular fluid for example is diminished, the concentration of sodium in the serum may be normal despite a deficit of this ion in the body Conversely a patient depleted of sodium may nevertheless have an abnormally high concentration of sodium in the serum if he be sufficiently dehydrated [69]

Having determined the nature of the fluid deficit or overload as the case may be one should proceed to correct same promptly The distortion may involve a deficit or excess of sodium or water or both The correction of each of these possibilities will now be considered

A deficit of water only is corrected by the administration of 10 per cent glucose in distilled water This condition of **dehydration** with high serum sodium is seldom encountered in patients with vomiting or diarrhea It will occur only if the patient has had no access to water and has lost no salt nor suffered any diminution in the extracellular fluid volume except that due to the water deficit

A **deficit of salt** only is observed in patients who have

lost salt but who have had access to water The volume of the extracellular fluid under these conditions may be normal or expanded and hyponatremia will usually be present In order to avoid abnormal expansion of the extracellular space this condition must be corrected by the administration of a 3 or 5 per cent solution of hypertonic saline The administration of 300 ml of 3 per cent sodium chloride provides enough sodium to raise the serum concentration of sodium in 11 liters 10 milliequivalents The same volume of a 5 per cent solution will do this for 21 extra liters In either case the extracellular volume will be increased only 300 ml [69]

In calculating the amount of sodium to be administered to correct an observed sodium deficit one may assume the volume of the total body water to be approximately two thirds of the body weight Accordingly a patient weighing 60 kgs whose serum sodium is to be raised from 128 meq per liter to normal (138 meq) would require

$_3 \times 60 \times 10 = 400$ meq NaCl
$400 \times 58\ 5$ (molecular weight of NaCl) $= 23400$ mgms
$= 23\ 4$ grams NaCl

This amount of salt is supplied by 780 ml of a 3 per cent or 468 ml of a 5 per cent solution Although sodium is retained in the extracellular space the volume of the total body water is used in the above calculation since water is withdrawn from the cells as the concentration of sodium in the extracellular fluid rises

If the volume of the extracellular fluid is decreased but its composition and tonicity are normal an amount of fluid equal to the estimated deficit is administered in the form of Ringer Lactate solution This is preferred over isotonic saline since it contains sodium and chloride in the proportions in which these are present in the extracellular fluid

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As an alternative solution (which has the advantage of being potassium free) one may utilize a solution containing two thirds normal saline and one third sixth molar lactate by volume

Correction of salt and water deficits as just outlined are made without difficulty Of equal concern but corrected less readily are **excesses of salt or water** with normal or expanded extracellular fluid volume The administration of water in a patient manifesting hypernatremia with a normal extracellular fluid volume will result in expansion of the latter and edema Likewise if the extracellular volume has been expanded with the development of hyponatremia administration of hypertonic salt solution merely perpetuates the overexpanded volume It is preferable in such a case to withhold all fluids to allow removal of the excess water from the body by the insensible perspiration This unfortunately is a slow process If these deviations are moderate they may be tolerated by the patient if however they cause considerable edema it may be necessary to resort to one of the artificial measures described later in order to correct the condition For this purpose intermittent peritoneal lavage with a solution having the composition shown in Table III and containing 5 to 7 per cent glucose has proven satisfactory

Infection is a common and serious complication of acute renal failure It is often present as a precipitating cause of the condition for example after abortion in papillary necrosis diabetic coma etc Intensive treatment with antibiotics or other chemotherapeutic agents is in such cases obviously necessary However even in the absence of evident infection the prophylactic administration of antibiotics is indicated throughout the course of the illness in order to avoid the appearance of infectious processes of which pneumonitis pleuritis, localized peritonitis interstitial nephritis

pyelonephritis endometritis and pyelophlebitis are most common As a **prophylactic,** aqueous crystalline penicillin in doses of 500 000 units should be administered once daily Should streptomycin or other toxic agents be used proper allowance should be made for the fact that in the absence of renal excretion excessively high levels of the drug are easily attained

THE PERIOD OF ANURIA

By the prompt use of the measures outlined in the preceding section the anoxia responsible for disruption of the renal tubules may be avoided or reduced to a minimum and any resulting renal failure will be of brief duration Unfortunately the fact that the patient is in shock is often not recognized so that correction of the condition is delayed or because of fear of overloading the circulation the intravenous injections of salt solutions are avoided when these are necessary

If the patient has been properly treated during the preliminary period of acute renal failure he should be in a relatively normal state as regards the **volume tonicity and composition** of his body fluids It is necessary then merely to maintain this status as constantly as possible during the subsequent period of anuria During this period therapeutic measures are directed at 1) maintaining a normal state of hydration and electrolyte balance 2) reducing the rate of endogenous protein catabolism to a minimum and 3) preventing infection peripheral vascular collapse and heart failure

In order to maintain a state of salt and water balance it would be desirable to measure the volume and determine the salt content of all the fluids lost from the body in the urine insensible perspiration vomitus stool and drainage from wounds or fistulae By administering a quantity of salt

and water equal to that lost from the above mentioned channels the patient would remain in salt and water equilibrium Such an exact balance is however usually not practicable

In order to avoid dehydration approximately one liter of 10 per cent glucose in distilled water (17 ml per kilogram of body weight) to allow for the loss by insensible perspiration is administered daily to maintain the patient in **water balance** In the presence of fever and in hot climates due allowance must be made for the increased loss of water by sweating as well as for the loss of salt by this route If no salt is being lost through sweating diarrhea vomiting fistulae or urine this administration of water alone should suffice to maintain normal extracellular fluid volume However this is rarely the case and it is desirable to determine the concentration of sodium in the serum as an aid in ascertaining the salt and water requirements Where marked distortions in extracellular volume occur these should be corrected promptly as described in the preceding section

Not only is the administration of excessive amounts of salt and water to be avoided during acute renal failure but it is necessary also to exclude the ingestion of protein since its utilization results in the accumulation of non protein nitrogenous waste products fixed acids and potassium none of which can be excreted During starvation energy is derived by the breakdown of fat and tissue protein, since the carbohydrate stores available to the organism suffice for its requirements for only a fraction of a day This breakdown of tissue protein amounts to about a gram per kilogram of body weight per day with the formation of approximately *165 mgms of non protein nitrogenous* waste product and corresponding amounts of fixed acids and potassium Since **carbohydrate** exerts a sparing action on the rate of endogenous protein utilization supplying the patient with this

foodstuff will reduce the rate at which tissue protein is metabolized Not only will this retard the rate of development of azotemia but what is more important it will decelerate the rate of rise of the serum concentration of potassium and the accumulation of fixed acids and other catabolites in the body The administration of a liter of 10 per cent glucose in water for example will furnish 400 calories which will avoid ketosis and will reduce the endogenous protein catabolism to approximately half of its starvation level If the entire caloric needs of the patient be met by a non protein diet (which can be done by the utilization of a glucose fat emulsion) the endogenous protein catabolism may be reduced to approximately one third of its starvation level *In this way it is possible for the patient without excretory function to continue for at least a month before* accumulating concentrations of non protein nitrogen above 300 mgms per cent [10, 89]

Various procedures have been advocated for administering the water salt and caloric requirements of the patient as just outlined Since nausea and vomiting are not uncommon in patients suffering from acute renal failure some consider it unwise to administer anything by mouth during the anuric period The administration of 10 per cent glucose in water plus any needed saline solutions by intravenous infusion is adequate in most patients Instead of glucose one may use a 10 per cent solution of invert sugar (in water or *when necessary in isotonic saline*) *which has the same* caloric value as a 10 per cent glucose solution but which may be given subcutaneously as well as intravenously A solution containing 50 ml of ethanol and 120 grams of invert sugar per liter is also well tolerated intravenously This contains 720 calories

If oral feedings are tolerated the fluid requirement may be met by administering a solution of sugar in water with

the addition of citric acid or lemon juice as a flavoring agent

In order to supply the 1600 to 2000 calories required for reducing endogenous protein catabolism to a minimum and maintaining a more normal state of nutrition several procedures have been advocated Borst[9] recommended the use of a mixture of flour (100 grams) sucrose (150 grams) and butter (100 grams) which furnishes 1750 calories daily He has also advocated a mixture of 150 grams of butter and 150 grams of sugar in the form of *chilled globules but this mixture is rarely acceptable and* may provoke nausea and vomiting Bernier[94] suggests sweet ened fruit juices with a small amount of well buttered bread and cakes Steamed rice or cream of wheat *well buttered* and sugared offers a high caloric intake with only minimal amounts of protein The simplest high caloric preparations are those originally recommended by Bull Joekes and Lowe[10] in which an emulsion of glucose (400 gm) oil (100 gm) and acacia (75 gm) in water (1 liter) plus vitamins are administered daily through a nasal tube How ever the discomfort of such a tube is objectionable and its use may lead to aspiration pneumonia which may prove lethal despite antibiotic therapy

A satisfactory **fat carbohydrate mixture** may be prepared extemporaneously by mixing an available oil (peanut pecan olive or coconut) with sucrose or glucose in an homogenizer with the addition of an emulsifying agent (polyethylene glycol) [84] Such a mixture containing 40 per cent fat and 10 per cent sugar is also available commercially and when flavored will often be tolerated when adminis tered orally in small frequent doses It contains 4 calories per ml so that the ingestion of 400 ml daily will furnish 1600 calories

The concentration of potassium in the serum as indi

cated in Chapter III is also a matter of concern during the period of anuria when abnormally low as well as high values may be encountered Because of the serious effects which such deviations induce on cardiac function they must be detected and corrected promptly

Hypopotassemia is remedied by the slow intravenous administration of a solution of 20 to 40 meq of potassium chloride per liter at a rate not to exceed 20 meq per hour Vials of potassium chloride containing 20 meq in 10 ml are available for this purpose and may be diluted with 5 per cent glucose in water More concentrated solutions of potassium chloride are to be avoided as their injection intravenously is painful Potassium deficits if not critical may also be repaired by the administration orally of tablets of potassium chloride in doses of 0 5 to 1 0 gram every two to three hours until a normal serum concentration is attained

The progressive development of an elevated concentration of potassium in the extracellular fluid with its resultant cardiotoxic effect is one of the principal hazards to be avoided during the course of acute renal failure [41] At serum concentrations above 5 5 meq per liter toxic effects are observed concentrations above 7 0 meq may be considered dangerous Several procedures have been used for reducing abnormal elevations in the serum potassium concentration As emergency measures the injection of glucose with insulin and of calcium salts to antagonize the cardiotoxic effects of potassium have been used with indifferent success The administration of glucose and an ample caloric intake in order to favor anabolic processes causes a transfer of potassium from extracellular spaces into the cells [7] Should this fail to maintain the concentration of potassium in the serum within normal limits it is necessary to remove the excess by some artificial measure Elkinton et al [20] recom

mend the use of carboxylic ammonium exchange resins (Amberlite XE 96) in the form of a 17 per cent suspension in water given orally or as a 10 per cent suspension injected into the rectum However since oral administration may provoke vomiting and the administration per rectum is uncertain in its effects and tends to augment the degree of acidosis the use of resins is less satisfactory than other artificial measures The artificial kidney has been used for this purpose with success[57] as has also intermittent peritoneal lavage [37, 66] as described later

Correction of the acidosis present in the anuric period by the administration of sodium bicarbonate or lactate (which is converted in the body to bicarbonate) has been widely advocated and practiced However, this is to be deprecated as potentially harmful Since the acidotic state is a result of the accumulation of fixed acids the administration of sodium salts can result only in an excess of sodium and expansion of the volume of the extracellular fluid with resulting edema Only in rare cases where bicarbonate is so depleted as to cause respiratory distress is the production of a sodium excess by the administration of alkali justifiable This is administered as sodium bicarbonate in doses of 1 or 2 grams orally every two to three hours or intravenously in the form of sixth molar sodium lactate until the desired effect is obtained Alkaline salts must be administered cautiously as they may precipitate tetany by reducing the concentration of ionic calcium If this occurs calcium chloride or gluconate should be administered intravenously In cases where the acidosis is accompanied by sodium deficit both deficiencies may be corrected simultaneously by the administration of sixth molar sodium lactate alone or in combination with sodium chloride if there is also a deficit of chloride

Metabolic acidosis as it is encountered in acute renal

failure is usually asymptomatic and requires no treatment Only in rare cases where bicarbonate is so depleted as to cause respiratory embarrassment is treatment necessary and in such cases the use of an artificial measure (e g peritoneal lavage) as described later is to be preferred to the use of alkaline solutions with resultant expansion of the extracellular space

Patients in acute renal failure are particularly prone to cardiovascular complications as described in Chapter III and should be observed carefully for evidence of heart failure and peripheral vascular collapse Cardiac failure may result from the administration of excessive amounts of fluid myocardial damage abnormalities in rhythm secondary to alterations in the potassium concentration of the serum or in association with the hypertension which may appear during the period of oliguria Treatment of these cardiovascular complications does not differ from that usually applied in heart failure Where congestive heart failure is present rapid digitalization and the administration of oxygen are indicated Acute pulmonary edema requires the use of digitalis oxygen (administered by positive pressure) *morphine aminophylline and venesection if necessary*

Among the minor procedures which have been recommended in the treatment of acute renal failure may be mentioned the use of **testosterone**[94] *in doses of 40 mgms* daily for its anabolic effects and the administration orally of **aluminum hydroxide** in order to eliminate phosphate from the bowel Although both procedures appear rational the need for either of them is questionable

THE PERIOD OF DIURESIS

With the onset of diuresis the same general principles govern treatment as during the period of anuria or oliguria However during this diuretic period great losses of salt and

water occur which necessitate the administration of large amounts of these substances in order to maintain a normal extracellular fluid volume Salt and water must be administered in amounts equal to those excreted by the kidney during this period This may entail the administration of 5 to 12 liters of water daily and an amount of salt equal to that excreted in the urine Unless the urinary losses are adequately replaced dehydration and a deficit of the extracellular fluid volume ensue *This in turn will lead to circulatory* insufficiency and a cessation once more of renal function

The volume of **water** required during this period may be readily calculated from the urinary output plus the estimated loss by insensible perspiration (17 ml per kgm of body weight per day) The **salt** required may be determined by analysis of the urine for its sodium and chloride content It is desirable also to follow the body weight and the sodium and chloride concentrations of the serum as indicators of the water and salt requirements

The period of **salt and water wastage** usually subsides in the course of three to 10 days However in some cases several months may elapse before the kidney is able to conserve salt and water and during this period these must be administered in amounts adequate to replace urinary losses The period of diuresis accordingly although heralded as a good omen and as an *indication of ultimate recovery* is actually a critical period requiring careful adjustment of salt and water exchange

The final period of **convalescence** is characterized by a progressive decline in the azotemia which disappears within 10 to 20 days As anorexia abates and the appetite returns feeding of a normal diet is resumed The maintenance of adequate nutrition with vitamin and mineral supplements is important at this period The capacity of the kidney to

concentrate urine maximally is the last tubular function to return to normal

ARTIFICIAL MEASURES

Although the majority of patients managed as outlined in the preceding sections recover without recourse to the use of the artificial measures now to be described these cannot always be dispensed with and their application may prove lifesaving The use of an artificial method (exchange trans fusion the artificial kidney peritoneal lavage) is indicated in patients who have been mismanaged during the period of anuria or who develop 1) generalized edema as a result of the injudicious administration of fluids with expansion of the volume of the extracellular fluid 2) pulmonary edema as a result of left heart failure and not responding to the usual medical measures 3) hyperpotassemia and 4) pro found acidosis Their use is also to be considered in severe intoxication with barbiturates or other diffusible toxins

A grossly elevated non protein nitrogen concentration per se is not an indication for instituting an artificial measure However in patients suffering from extensive tissue destruction the rate of rise of the non protein nitrogen concentration with concomitantly marked changes in the other blood chemical findings may be so rapid as to require the use of an artificial measure to restore a more normal internal environment and to permit survival for the period necessary for regeneration of the tubules Although urea and the other non protein nitrogenous constituents are rela tively non toxic the changes accompanying a rise in the non protein nitrogen concentration of the blood above 400 mgms per cent are such that most patients are in a pre carious state when this occurs By careful observation one must determine when the use of an artificial measure is in dicated

With the availability of peritoneal lavage as a simple easily applicable method or in the few institutions where an artificial kidney is available it is preferable to utilize one of these measures when the need arises rather than risk a fatal outcome

The artificial measures which have received application are 1) exchange transfusion 2) irrigation of the bowel 3) the artificial kidney and 4) peritoneal lavage The first three of these will be described only briefly since for de tailed information concerning their use the original papers must be consulted the last named because of its easy and general applicability will be described in greater detail

Exchange Transfusions

In exchange or exsanguinating transfusions an attempt is made to replace the blood of the patient with normal blood This procedure has been used most extensively in France[94] Although simple in theory it is inefficient and costly and much inferior to the procedures to be described later The exchange of 10 liters of blood for example in a man weighing 60 kgs whose blood urea level is 500 mgms per cent will result in the removal of only 40 grams of urea or less than a sixth of that present in the body The reputed presence within the blood stream of non diffusible toxic agents not removed by the procedures to be discussed later has not been substantiated and hence offers no argument in favor of exchange transfusion

In exchange transfusion as performed in over 600 pa tients at the *Centre Regional de Transfusion Sanguine*[94] the blood of the recipient and donor are carefully cross matched in the AB O and Rh systems and a search made for the presence of irregular agglutinins Five to 10 liters of citrated blood obtained from 13 to 25 donors is slowly infused intravenously while an equivalent amount is with

drawn from a distant vein The usual reactions to trans fusion may be encountered as well as hypocalcemia and hypernatremia due to the large volumes of sodium citrate used as anticoagulant The latter may be avoided by the use of heparin

Irrigation of the Bowel

Continuous lavage of some segment of the bowel has been suggested as a means of treating acute renal failure [39, 53] However this method has met with little success for not only is it relatively inefficient but it is also difficult to control the exchange of water and electrolyte across the bowel Odel and Ferris[63] introduced the perfusing solution into the duodenum through a nasal tube and removed it in part through a catheter inserted through the exteriorized ap pendix and attached to a continuous suction apparatus and in part through a drainage tube placed in the rectum The same authors as had Kolff[45] before them also irrigated the colon through a catheter passed into the rectum This method removed little urea and the patient developed pul monary edema

Maluf[54] passed the irrigating fluid (2 to 2 3 per cent sodium sulfate) through a nasal tube into the upper jejunum and removed it by a tube passed into the rectum A second nasal tube removed any fluid regurgitating into the stomach Although effecting a notable decrease in the urea content of the blood there was also a marked loss of extracellular fluid and of sodium chloride calcium and potassium from the body

The gastrointestinal tract is apparently unsuited for use as a semipermeable membrane Unlike the peritoneal mem brane across which a predictable and rapid exchange takes place the bowel alters solutions placed within it in an un predictable manner The apparent decline of the urea con

centration of the blood and the improvement in the clinical appearance of patients in uremia following gastric lavage[94] is attributable to the incidental hydration which such patients undergo The negligible amount of urea removed by this process is an indication of its inefficiency[39, 93]

The Artificial Kidney

The earliest attempts at **hemodialysis** were those of Abel Rowntree and Turner who in 1914 utilized a series of collodion tubes through which blood from a dog was allowed to circulate Hirudin was used as an anticoagulant Kolff[46] in 1944 first applied an artificial kidney to the human Details of his procedure and apparatus have been modified by subsequent workers[56, 9] The apparatus most widely used at present and available commercially is that shown in Figure 4 It consists essentially of a device which permits the passage of the patient s blood through a dialyzing membrane across which nitrogenous and other waste products diffuse The membrane which is wound about a revolving drum consists of 100 feet of cellophane tubing which is detoxified by prolonged boiling and filled with blood compatible with that of the patient The radial artery and a large vein of the patient are cannulated and connected with the apparatus which is equipped with the necessary pumps air traps filters and temperature controls Coagulation of the blood is prevented by the injection intravenously at regular intervals of 100 mgms of heparin

The artificial kidney of the Kolff type removes efficiently the non protein nitrogen and other waste products from the body the concentration of which may be reduced to half their initial values by a five hour period of dialysis The potassium and other electrolyte concentrations also approach those of the bath fluid so that by adjusting the ionic composition of the latter one can correct any abnormal

electrolyte pattern of the blood Glucose (3 per cent) is added to the bath fluid to prevent absorption of fluid by the body

The use of the artificial kidney is limited to the relatively few institutions where a well trained team acquainted with

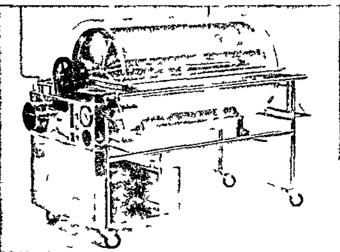


Figure 4 A commercially available model of the mechanical kidney of the Kolff type (Photograph reproduced by permission of the Allis Chalmers Manufacturing Co Milwaukee Wisconsin through the courtesy of Dr J T Jarman)

its manipulation is available [56] It is too expensive and complicated for general application particularly since a simple method (peritoneal lavage) requiring no special and expensive apparatus and which is more easily applied and equally effective is available for clinical use [37] Although simple in principle many factors complicate the use of the artificial kidney [95] e g the potential toxicity of the membrane the difficulty in avoiding alterations in extracellular fluid volume the need for anticoagulants a trained group

of operators and blood to fill the dialyzing membrane These all mitigate against its use in the infrequent occasions when some extrarenal device is needed in the management of acute renal failure

More compact models of the artificial kidney have been suggested and in some cases applied to the human In the apparatus of Murray[51, 64] and of Alwall [3, 4] the membrane is placed on the inner of two closely aligned cylinders and bathed in a circulatory bath fluid The modification devised by Moreau and used by Bessis and Freixa[94] consists of a series of units in which the cellophane is placed within a glass container In the apparatus of Skeggs and Leonards [94] a layer of sheet cellophane is placed between corrugated rubber pads which separate the blood from the perfusing liquid An apparently simple apparatus recently suggested by Guarino[39] consists of 23 feet of three quarter inch cello phane tubing arranged in concentric layers with the free ends connected to a reservoir containing the continuously circulated rinsing fluid However thus far neither it nor the apparatus of Skeggs and Leonards have proven suitable for application to the human

Intermittent Peritoneal Lavage

The method of intermittent peritoneal lavage is safe and relatively simple in operation requires only generally avail able materials for its application and is sufficiently efficient to render it the method of choice of the various artificial measures available for use in acute renal failure It will accordingly be described in sufficient detail to permit its application by the reader

Peritoneal lavage is a procedure that has long been ad vocated for use in renal failure It was described in great detail by Fine Frank and Seligman[3, 89] in 1946 and uti lized in the form advocated by these workers or in various

modifications by many subsequent workers[1] In a review of the subject by Odel Ferris and Power[66] in 1950 references in the literature to 101 patients treated by this procedure were collected Numerous accounts of its satisfactory application have been reported but these reports of its effectiveness are not all convincing Moreover the method has often proved disastrous since patients subjected to it often developed pulmonary edema or peritonitis for which reason it was not acceptable as a satisfactory or safe procedure

Experimental studies by the author have demonstrated that continuous peritoneal lavage as performed by earlier workers is unnecessarily complicated A modified intermittent procedure is not only efficient and simpler but also avoids the pulmonary edema and infection which rendered the previous methods unsatisfactory It was shown in the first place that a period of several hours is required for fluid present in the peritoneal cavity to reach equilibrium with the blood It is accordingly unnecessary to use a continuously circulating stream of fluid By inserting and removing the fluid intermittently the need for complex drains or the use of large volumes of fluid is avoided[3]

The peritoneum presents an efficient dialyzing membrane with a filtering surface of approximately 22 000 square centimeters which is comparable to that of the renal glomeruli Solutions placed within the peritoneal cavity enter into physico-chemical equilibrium with the blood It is thus possible to utilize the peritoneum rather than an artificial extracorporeal apparatus as a means of removing urea and other catabolites from the body as well as to alter the composition of the blood to conform to that of a solution placed in the peritoneal cavity By adjusting the osmotic pressure of the lavaging fluid by the addition of glucose it is also possible to control the passage of fluid to and from the cir

culation By adjusting the electrolytes and the glucose content of the lavaging fluid and the time during which this is allowed to remain in the abdominal cavity it is thus possible to adjust the volume of the extracellular fluid as well as its composition The procedure can be used moreover with the facilities available in any hospital and without technical difficulty

In intermittent peritoneal lavage the lavaging fluid is introduced and removed through a small **polyethylene medical tube,** which causes no tissue reaction and does not adhere to the omentum Tubing of an internal diameter of 0 115 and an outside diameter of 0 147 inch is satisfactory A series of small holes may be placed in the end of the tube by means

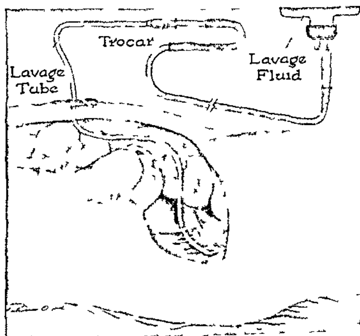


Figure 5A (*Legend on opposite page*)

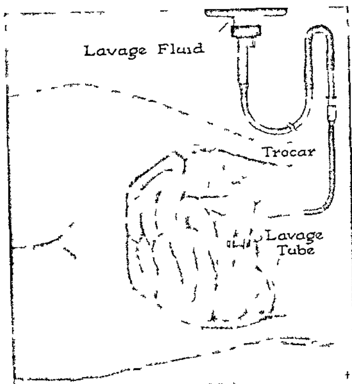


Figure 5B A cross sectional view illustrating the technique of intermittent peritoneal lavage as described in the text In A the patient is shown in the supine position in B in the lateral position Note the position of the polyethylene lavage tube which is passed through a paracentesis trocar inserted just below the umbilicus The lavage fluid is suspended about a meter above the patient rather than as shown in the figure

of a heated needle and a suitable length of the material (approximately twelve to eighteen inches) is kept ready for use by immersion in a bland germicidal solution This tube is introduced into the peritoneal cavity through an ordinary

paracentesis trocar After a local anesthetic is injected under the skin the trocar is inserted either in the mid line below the umbilicus or laterally along the transversalis muscles After removing the stylet from the trocar the polyethylene tubing is introduced and directed into the pelvis Care should be taken not to introduce it so far that it curls back upon itself its end should occupy the lowermost point in the pelvic gutter The position of the tube and the manner in which the fluid is introduced into the abdomen is illustrated in Figure 5

The **lavaging fluid** is prepared extemporaneously from commercially available solutions and magnesium chloride The latter is prepared by dissolving 17 grams of chemically pure $MgCl\ 6H_2O$ in 100 ml of pyrogen free water and sterilizing the solution in an autoclave The ionic composition of the lavaging fluid is shown in Table III it is essentially that of an ultrafiltrate of plasma and may be prepared by adding the amounts of the commercially available solutions indicated in the third column of Table III to a sterile bottle and bringing the final volume up to 1000 ml by adding 300 ml of 10 per cent glucose in water This concentration of glucose exerts the osmotic force necessary for preventing absorption of the fluid during the one and one half to two hours that it remains in the abdomen If it is necessary to remove fluid from the patient a more concentrated glucose solution (5 to 10 per cent) is used This is prepared by adding the necessary amount of 50 per cent glucose If it is desired to hydrate the patient less glucose (1 gram per liter) is used In addition to the electrolytes and glucose 100 000 units of crystalline penicillin or 25 mgms of terramycin hydrochloride are added to each liter as a prophylactic against infection

The lavaging fluid is allowed to flow into the body cavity by gravity as shown in Figure 5 For the average sized adult

TABLE III

IONIC COMPOSITION OF THE IRRIGATING FLUID USED IN INTERMITTENT PERITONEAL LAVAGE

	Grams per liter	ml of available solutions	Ionic Composition *Milliequivalents per liter* Na+	K	Ca++	Mg	Cl	HCO
Sodium Chloride	6 00	660 cc of 0 9 per cent saline	103				103	
Sodium Bicarbonate	3 00	40 cc of 3 75 grams in 50 cc ampoule	36					36
Potassium Chloride	0 30	cc of 14 9% solution		4 0			4 0	
Calcium Chloride	0 5	? 5 cc of 10% solution			4 5		4 5	
Magnesium Chloride Hexahydrate	0 17	1 cc of 17% solution				1 7	1 7	
		TOTAL	139	4 0	4 5	1 7	113 ?	36

*The potassium chloride is omitted in cases of hyperpotassemia

To the above solution is added 100 000 units of crystalline penicillin 25 mgms of terramycin and sufficient 10 per cent glucose in water to make a liter The calcium and magnesium salts and the antibiotics are added just before injecting the fluid into the peritoneum in order to avoid precipitation of the former as carbonate and destruction of the latter

The solution prepared as indicated in Table III has a higher chloride and bicarbonate content than normal blood plasma in order to correct more rapidly the deviations encountered in renal failure However where the dialysis is performed for long periods a solution having the electrolyte composition of an ultrafiltrate of normal blood plasma must be used in order to maintain normal blood levels This may be prepared by using only ? grams (26 7 cc) of sodium bicarbonate and 580 cc of 0 9 per cent sodium chloride instead of the amounts indicated in Table III and adding in addition to the other salts listed in the Table 144 cc of sixth molar sodium lactate The resulting solution has a composition approximating that of normal blood plasma viz Na^+ 138 mEq K^+ 4 0 mEq Ca^{++} 4 5 mEq Mg^{++} 1 7 mEq Cl^- 100 mEq and HCO^- 24 mEq It is possible by altering the composition of the lavaging fluid to correct any observed deviations and attain more rapidly the desired composition Thus in patients manifesting hypernatremia a solution containing only 130 mEq of Na^+ would promptly reduce the blood sodium content to normal.

2 to 3 liters of fluid are introduced at one time the amount being such as to cause no appreciable discomfort to the patient by distention of the abdomen In children correspondingly smaller amounts (0 5 to 1 5 liters) are used depending on their size

The solution is allowed to remain in the peritoneal cavity *for one and one half hours to permit its entering into* equilibrium with the blood The polyethylene tube is then connected through a sterile rubber tube with a bottle placed on the floor beside the bed of the patient and the fluid allowed to siphon off A small deficit in the volume recovered may occur after the first instillation as a result of trapping of fluid in the coils of the intestines but this is usually negligible The over all volume of fluid recovered should be equal to that inserted into the peritoneal cavity In cases where absorption of fluid has occurred this may be recovered by increasing the glucose content of the solution (to 5 per cent or more) and withdrawing it after about an hour or less By using such high concentrations of glucose fluid *may also be rapidly withdrawn from the body in cases of* pulmonary or systemic **edema** In patients with **hyperpotassemia**, a solution having the composition of that shown in Table III but from which potassium chloride has been omitted is used

Because of its ease and safety of application intermittent peritoneal lavage as just described may be used in patients requiring an artificial measure to restore the normal composition volume and tonicity of the body fluids For most purposes 6 to 12 exchanges with 2 to 3 liters at two hourly intervals suffice to restore a sufficiently normal state to permit resumption of the conservative regime described earlier By allowing the polyethylene tube to remain in the peritoneal cavity one may resort to the use of peritoneal lavage again should this become necessary later

SEVEN

EPILOGUE

THE INCIDENCE OF ACUTE RENAL FAILURE AND THE FREquency with which it contributes to a fatal outcome is difficult to estimate since the primary cause of this complication usually overshadows the renal defect However it is undoubtedly a common occurrence Recognition and prompt treatment of the acute circulatory failure particularly the extracellular volume deficit which characterizes shock will reduce the incidence of acute renal failure to a minimum and should be uppermost in the mind of the surgeon or practitioner who first encounters the patient suffering from any serious disorder It must be remembered that hypotension is a late symptom of circulatory shock and its appearance should not be awaited before restoring depleted blood and extracellular fluid volume The occurrence of oliguria must be noted at its inception so that conservative medical management may be instituted promptly Facilities should be on hand for the application of an artificial measure when this be necessary On the basis of our present knowledge acute renal failure should become a rare occurrence with a low mortality except in such cases where it is merely an accompaniment of irreversible and fatal damage elsewhere than in the kidney

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